PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/445, 31/57 // (A61K 31/57, 31:445) — A1

(11) International Publication Number: **WO 00/51605**

(43) International Publication Date: 8 September 2000 (08.09.00)

(21) International Application Number: PCT/US99/04502

(22) International Filing Date: 1 March 1999 (01.03.99)

(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LUGO, Sergio Ulloa [MX/MX]; Rinconada de Sn. Buena, Ventura 33, Club de Golf, Tlalpan, Mexico, D.F. 14620 (MX). RAMOS, Jose Villacampa [MX/MX]; Prol. Uxmal 1074-502B, P.Ma, Anaya, Mexico, D.F. 03340 (MX). ARELLANO, Sergio Morales [MX/MX]; Rosario Castellanos 112A, Culhuacan, Coyoacan, Mexico, D.F. 04480 (MX). MICHEL, Olivier [FR/FR]; 50, avenue Georges Pompidou, F-69003 Lyon (FR).

(74) Agents: KALYANARAMAN, Palaiyur, S. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: COMPOSITIONS AND METHODS FOR TREATING ATOPIC DERMATITIS, ANGIOEDEMA AND OTHER DISORDERS USING ANTIHISTAMINES AND GLUCOCORTICOIDS

(57) Abstract

Disclosed herein are compositions and methods for treating atopic dermatitis, angioedema, urticaria, allergic rhinitis and other such disorders. The compositions comprise therapeutically effective amounts of antihistamines such as, for example, loratadine, and glucocorticoids such as, for example, betamethasone, for such treatment.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

COMPOSITIONS AND METHODS FOR TREATING ATOPIC DERMATITIS, ANGIOEDEMA AND OTHER DISORDERS USING ANTIHISTAMINES AND GLUCOCORTICOIDS

FIELD OF THE INVENTION

The present invention generally relates to compositions and methods for treating atopic dermatitis, angioedema, urticaria, allergic rhinitis and other such disorders. It specifically discloses compositions comprising therapeutically effective amounts of antihistamines such as, for example, loratadine, and glucocorticoids such as, for example, betamethasone, for such treatment.

BACKGROUND OF THE INVENTION

Atopic dermatitis is a chronic, itching, superficial inflammation of the skin, usually found in individuals with a history of allergic disorders. (*The Merck Manual of Diagnosis and Therapy*, D. Holvey ed., published by Merck & Co., Inc., Rahway, New Jersey, (1972) 1460). Angioedema and urticaria are local wheals and erythema in the dermis and can be due to causes such as, for example, drug allergy, insect bites and the like, *ibid*, page 241. Atopic dermatitis is generally managed by applying ointments or pastes of topical corticosteroids. Itching is generally relieved by antihistamines, often in large doses. Initially useful medicaments may generally become ineffective and must be replaced. Acute urticaria is often managed by oral antihistamines; corticosteroid treatment may be occasionally necessary particularly when associated with angioedema. Topical corticosteroids are generally of no value.

Products containing a combination of a steroid and an antihistamine are known and available. For example, a product containing chlorfeniramine maleate and paramethasone is available under the tradename DILARMINE® from Roche Pharmaceuticals, Nutley, New Jersey. However, the antihistamines in such products are typically sedating. There may be situations where sedating antihistamines are not acceptable.

It would be desirable to find effective pharmaceutical compositions and methods of treatment for diseases such as atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, allergic reaction to insect stings and bites and other such disorders.

It would be especially desirable to find compositions and methods of treatment for such diseases using an effective amount of a combination of one or more

antihistamines, which are substantially non-sedating, with one or more glucocorticoids.

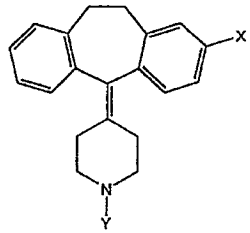
It would be additionally desirable to have such a combination composition and methods of treatment where the selected substantially non-sedating antihistamine(s) and glucocorticoid(s) are safe with low potential for systemic toxicity.

Other desires, objectives and advantages of the present invention will be apparent to those skilled in the art from the accompanying description and claims.

DESCRIPTION OF THE INVENTION

The above-noted desires and objectives are addressed by the present invention which, in one embodiment, provides pharmaceutical compositions to treat diseases such as, for example, atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, allergic reaction to insect stings and bites and other such disorders. The composition comprises in combination: (i) a therapeutically effective amount of one or more substantially non-sedating antihistamines or a pharmaceutically acceptable salt or solvate of such antihistamine(s) and (ii) a therapeutically effective amount of one or more glucocorticoid or a suitable derivative thereof. The present invention additionally discloses a method for the treatment of the above-noted diseases in a mammalian organism in need of such treatment, such treatment comprising administering a pharmaceutical composition described above.

The antihistamines useful in the practice of the present invention correspond to the general Formula I:



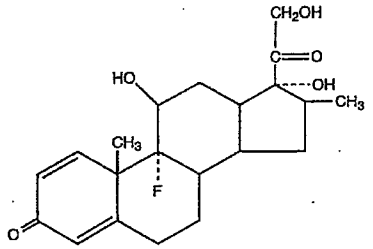
Formula I

wherein X represents a halogen atom or a hydrogen atom; and Y represents hydrogen, $-COOR_1$ or $-SO_2R_2$, wherein R_1 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted

alkenyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heterocyclic ring; and R_2 represents a substituted or unsubstituted cycloalkyl group, or substituted or unsubstituted aryl group. The term "substituted" refers to appropriate substitution with moieties such as, for example, alkyl, aryl, aralkyl, alkylaryl, cycloalkyl, heterocyclic, halogen, ester, amide, ether, carbonyl, sulfonyl and the like. The compounds of Formula I embrace optical isomers and mixtures thereof, racemic mixtures, enol forms and other such modifications. Preferred compounds belonging to Formula I are those in which X is a halogen atom or a hydrogen atom, and Y is hydrogen or -$COOR_1$, where R_1 is defined above. More particularly preferred compounds of this class are when X is Cl and R_1 is carboethoxy (the compound being commonly known as loratadine) and when X is Cl and R_1 is hydrogen (the compound being commonly known as descarboethoxyloratadine or desloratadine or DCL). The compounds of Formula I can be prepared in accordance with processes known in the art, for example, that disclosed in U.S. Patents 3,326,924 and 4,282,233. DCL is described, for example, in U.S. Patent 4,659,716 and is a metabolic derivative of loratadine.

Glucocorticoids generally belong to a class of steroid hormones that are synthesized by the adrenal cortex of vertebrates and have anti-inflammatory activity. Many are well known. The glucocorticoids useful in the practice of the present invention include, for example, prednisolone, prednisone, betamethasone, dexamethasone, fluoromethalone, medrysone, triamcinolone; hydrocortisone, prednicarbate, deflazacort, halomethasone, tixocortol, predinylidene (21-diethylaminoacetate), prednival, paramethasone, methylprednisolone, meprednisone, mazipredone, isoflupredone, halopredone acetate, halcinonide, formocortal, flurandrenolide, fluprednisolone, fluprednine acetate, fluperolone acetate, fluocortolone, fluocortin butyl, fluocinonide, fluocinolone acetonide, flunisolode, flumethasone, fludrocortisone, enoxolone, difluprednate, diflucortolone, diflorasone diacetate, desoxymetasone, desonide, cortivazol, corticosterone, cortisone, cloprednol, clocortolone, clobetasone, clobetasol, chloroprednisone, cafestol, budesonide, beclomethasone, amcinonide, allopregnane acetonide, alclometasone, 21-acetoxypregnenolone, tralonide, diflurasone acetate, deacylcortivazol, budesonide, deacylcortivazol oxetanone, and the like. Several of these compounds are known glucocorticoids and many are described in *The Merck Index*, Twelfth Ed., Merck & Co., Inc., Rahway, New Jersey (1996). Preferred glucocorticoids include betamethasone, prednisolone, prednisone, flumethasone and hydrocortisone. Most preferred is betamethasone.

Loratadine has been extensively studied for its antihistaminic effects and is considered to be a safe antihistamine as a H_1 antagonist. It is also considered to be an antihistamine without clinically significant sedative effects. It has also been proven to be safe and effective for the treatment of several respiratory and dermatologic allergic diseases. Betamethasone (Formula II) is a synthetic fluorinated derivative of hydrocortisone and has antiinflammatory properties. Betamethasone has been



Formula II

extensively used in clinic, as well as as a corticosteroid reference in several clinical trials. A discussion can be found in, for example, A, Munck *et al*, "Physiological Functions of Glucocorticoids in Stress and their Relation to Pharmacological Actions", *Endocr. Rev.*, Vol. 5 (1984), 25-44. A combination of an antihistamine such as loratadine and a glucocorticoid such as betamethasone has now been found to be a highly effective medicament for treating allergic and related diseases stated above without having a sedating effect.

As stated above, the present invention generally discloses novel pharmaceutical compositions comprising a substantially non-sedating antihistamine and a glucocorticoid. Additionally, there may be other optional ingredients present such as, for example, a pharmaceutically acceptable carrier. Still additional ingredients may also be present, especially depending on the form of administration of the pharmaceutical composition, as detailed later. The antihistamine or its pharmacologically acceptable salt or solvate is generally present in the composition in about 2-20 milligrams per dosage, preferably in about 2-10 milligrams and typically in about 3-7 milligrams. The glucocorticoid is generally present in the composition in about 0.02-1 milligram per dosage, preferably in about 0.02-0.8 milligrams and typically in about 0.03-0.5 milligram. Preferably the weight ratio of the glucocorticoid and antihistamine is in the range between about 1:100 and 1:10.

As stated earlier, a pharmaceutically acceptable carrier (which includes diluents, excipients or carrier materials) may also be present in the composition. The carrier is suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, solutions, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active ingredients (i.e., the antihistamine and the glucocorticoid) may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents, disinfectants and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Suitable lubricants that may be mentioned for use in these dosage forms include, for example, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Disinfectants include benzalkonium chloride and the like. Sweetening and flavoring agents and preservatives as well as other ingredients such as, for example, sodium croscarmellose, may also be included where appropriate.

In another embodiment, the present invention discloses a method of preparing a composition for use in the treatment of diseases such as, for example, atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, allergic reaction to insect stings and bites and other such disorders, with the composition comprising a therapeutically effective amount of one or more substantially non-sedating antihistamines, or a pharmaceutically acceptable salt or solvate of such antihistamine, and one or more therapeutically effective glucocorticoid, optionally in combination with a pharmaceutically acceptable carrier.

In yet another embodiment, the present invention discloses a method of administering an effective treatment for diseases such as, for example, atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, allergic reaction to

insect stings and bites and other such disorders, the administration comprising administering a pharmaceutical composition described above. The pharmaceutical compositions of the present invention can be administered depending upon the patient's age, sex, weight and severity of the condition being treated. Generally, the human oral dosage form containing the antihistamine and the carrier can be administered 1 or 2 times per day.

In a further embodiment, this invention discloses a method for the treatment of diseases such as, for example, atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, allergic reaction to insect stings and bites and other such disorders in a mammalian organism in need of such treatment, such treatment comprising administering a therapeutically effective amount of one or more substantially non-sedating antihistamines, or a pharmaceutically acceptable salt or solvate of such antihistamine, and one or more therapeutically effective glucocorticoid, optionally in combination with a pharmaceutically acceptable carrier.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Dosage form - refers to composition containing the antihistamine, the glucocorticoid and optionally a carrier formulated into a delivery system, i.e., tablet, capsule, oral gel, powder for constitution or suspension in association with inactive ingredients.

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients and optionally the carrier. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression

of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gels-refers to the active ingredients and the carrier dispersed or solubilized in a hydrophilic semi-solid matrix.

Powders for constitution refers to powder blends containing the active ingredients and the carrier and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 2 to about 98% by weight of the total composition.

Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as croscarmellose sodium; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 1 to about 15% by weight of the composition.

Binders - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn, rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as cellulose, methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 98% by weight of the composition.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium

acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.05 to about 5% by weight of the composition.

Glidents - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control, as well as to topical bioavailability.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures.

The phrase "therapeutically effective amount" means that amount of the active ingredients which provides a therapeutical benefit in the treatment or management of the diseases stated above by the present inventive composition.

The magnitude of a prophylactic or therapeutic dose of the active ingredients in the acute or chronic management of the targeted disease or condition will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according the age, body weight, and response of the individual patient. Suitable total daily dose ranges can be readily determined by those skilled in the art. The dose may be administered in single or divided doses orally, topically, transdermally, or locally by inhalation.

It is further recommended that children, patients aged over 65 years, and those with impaired renal or haptic function initially receive low doses, and that they then be titrated based on individual response(s) or blood level(s). Further, it is noted that the clinician or treating physician will know how and when to adjust, interrupt, or terminate therapy in conjunction with individual patient response.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the active ingredients according to the methods of

the present invention. Some such routes are, for example, oral, intraoral, rectal, parenteral, epicutaneous, transdermal, subcutaneous, intramuscular, intranasal, sublingual, intradural, intraocular, intrarespiratory, oral or nasal inhalation and the like. Oral administration is preferred.

The term "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids or bases or organic acids or bases. Examples of such inorganic acids are hydrochloric, hydrobromic, hydriodic, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, algenic, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example, from N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucaine), lysine and procaine. A similar meaning is given to the term "pharmaceutically acceptable solvate" which, however, includes a solvent, water and the like as the solvating medium.

As stated before, dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, syrups, elixirs, gels, powders, magmas, lozenges, ointments, creams, pastes, plasters, lotions, discs, suppositories, nasal or oral sprays, aerosols and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desirable, tablets may be coated by standard aqueous or nonaqueous techniques. Another preferred dosage form is as liquid or solution, comprising the active ingredients along with any additional optional ingredient or ingredients in a pharmaceutically acceptable carrier which is preferably a liquid.

Pharmaceutical compositions for use in the methods of the present invention may be prepared by any of the methods of pharmacy, but all methods include the step or steps of bringing into association the active ingredients and any optional ingredient or ingredients, carrier and the like. Generally stated, the compositions are prepared by uniformly and intimately admixing the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

An example composition containing loratadine and betamethasone for a tablet and preparation of a tablet by a compression molding process may be illustrated as in the following Table I:

Table I

Name of the Ingredient	Concentration range (milligram/tablet)
Betamethasone	0.1-0.5
Loratadine	2-10
Lactose monohydrate (LACTOSE FASTFLO®)	55-290
Sodium Croscarmellose	0.8-4
Magnesium stearate	0.4-1
Tablet weight:	60-300 mg.

The above-stated ingredients may be admixed in any suitable order and converted into a tablet by suitable methods such as, for example, the methods stated earlier. Thus, in one example, betamethasone (0.25 mg) and loratadine (5 mg) were premixed with one portion (70 mg) of Lactose FASTFLO® (available from Foremost Farm USA, Baraboo, Wisconsin). The mix was then passed through a Quadro CoMil® mill (a sieve mill available from Quadro, Waterloo, Ontario, Canada) equipped with a 20 mesh screen. The remaining portion of lactose FASTFLO® (71.75 mg) and croscarmellose sodium (2 mg) were then added and blended. Magnesium stearate (1 mg) was then mixed in and blended well. The mixture was then compressed in a rotary tablet press to make tablets. A tablet weighing about 150 milligrams may be prepared with the above-noted composition.

Alternatively, a tablet may be prepared by a wet granulation method. An example composition containing loratadine and betamethasone for a tablet and preparation of a tablet by a wet granulation process may be illustrated as in the following Table II. In Table II, AVICEL PH301® is a microcrystalline cellulose, available from FMC Corporation Pharmaceutical Division, City of Industry, California; Kollidon VA64® is a modified polyvinyl pyrrolidone available from BASF Mexicana S.A de C.V. Av, de los Deportes C.P., Mexico D.F.; Kollidon CL® is

another modified polyvinyl pyrrolidone also available from BASF Mexicana S.A de C.V. Av, de los Deportes C.P., Mexico D.F.

Table II

Name of the Ingredient	Concentration range (milligram/tablet)
Betamethasone (micronized)	0.1-0.5
Loratadine (micronized)	2-10
Cellulose microcrystalline (e.g., AVICEL PH301®)	55-290
Kollidon VA64®	1-5
Kollidon CL®	2-10
Magnesium stearate	0.1-1
Ethyl alcohol	as needed (about 20-40 weight % based on total formulation)
Tablet weight:	100 mg

In the illustrative process, in a suitable container, sufficient alcohol was taken to dissolve loratadine (5 mg), betamethasone (0.25 mg) and Kollidon VA64® (3 mg) and the three ingredients were dissolved in it. In a separate mixer, cellulose (84.65 mg) and Kollidon CL® (7 mg) were mixed for about 15 minutes and this mix was then blended and granulated with the alcohol solution and mixed until a uniform granulate was formed. The granulate was then spreaded on trays and dried in an oven until a 1.5-2.5% moisture level was obtained. The granulate was then passed through a 25 mesh screen, charged into a mixer and mixed well with magnesium stearate (0.1 mg) for about 2 minutes. This mix was then compressed into tablets using a tablet press machine and 4 inch deep concave round punches.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the invention and appended claims. Furthermore, even though the above-stated illustrative examples are prepared using loratadine and betamethasone as the active ingredients, it should not be considered as limiting the scope of the invention in any way; other suitable substitution of the active ingredients may be made using the earlier stated lists of suitable compounds. Modifications of the active ingredients and the other ingredients as well as the process suitably are also to be considered as falling within the scope of the invention, description and appended claims.

CLAIMS

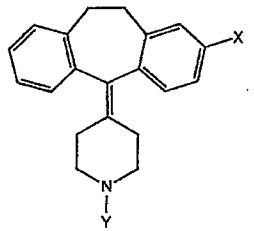
What is claimed is:

1. A pharmaceutical composition for treating atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, and allergic reaction to insect stings and bites, said composition comprising: (i) a therapeutically effective amount of one or more substantially non-sedating antihistamines or a pharmaceutically acceptable salt or solvate thereof; and (ii) a therapeutically effective amount of one or more glucocorticoid.

2. The composition of claim 1 for treating atopic dermatitis.

3. The composition of claim 1 for treating angioedema.

4. The composition of claim 1, wherein said antihistamine corresponds to the general formula:



wherein X represents a halogen atom or a hydrogen atom; and Y represents hydrogen, $-COOR_1$ or $-SO_2R_2$, wherein R_1 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heterocyclic ring; and R_2 represents a substituted or unsubstituted cycloalkyl group, or substituted or unsubstituted aryl group as well as optical isomers and mixtures of said antihistamine, with said substituents being a C1-C6 alkyl, aralkyl, alkylaryl, aryl and cycloalkyl.

5. The composition of claim 4, wherein X is a halogen and Y is hydrogen or $-COOR_1$, wherein R_1 is the same as in claim 4.

6. The composition of claim 5, wherein X is Cl and Y is $-COOC_2H_5$, said antihistamine being known as loratadine.

7. The composition of claim 5, wherein X is Cl and Y is hydrogen, said antihistamine being known as desloratadine.

8. The composition of claim 1, wherein said glucocorticoid is selected from the group consisting of prednisolone, prednisone, betamethasone, dexamethasone, fluoromethalone, medrysone, triamcinolone, hydrocortisone, prednicarbate, deflazacort, halomethasone, tixocortol, predinylidene (21-diethylaminoacetate), prednival, paramethasone, methylprednisolone, meprednisone, mazipredone, isoflupredone, halopredone acetate, halcinonide, formocortal, flurandrenolide, fluprednisolone, fluprednine acetate, fluperolone acetate, fluocortolone, fluocortin butyl, fluocinonide, fluocinolone acetonide, flunisolode, flumethasone, fludrocortisone, enoxolone, difluprednate, diflucortolone, diflorasone diacetate, desoxymetasone, desonide, cortivazol, corticosterone, cortisone, cloprednol, clocortolone, clobetasone, clobetasol, chloroprednisone, cafestol, budesonide, beclomethasone, amcinonide, allopregnane acetonide, alclometasone, 21-acetoxypregnenolone, tralonide, diflurasone acetate, deacylcortivazol, budesonide, deacylcortivazol oxetanone, and mixtures thereof.

9. The composition of claim 8, wherein said glucocorticoid is betamethasone.

10. The composition of claim 1, additionally containing one or more ingredients selected from the group consisting of a pharmaceutically acceptable carrier, binder, lubricant, disintegrating agent, disinfectant, coloring agents, flavoring agent and preservative.

11. The composition of claim 10, wherein said additional ingredient is a pharmaceutically acceptable carrier.

12. The composition of claim 11, wherein said pharmaceutically acceptable carrier is selected from the group consisting of lactose, sucrose, sugar, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, ethyl alcohol and mixtures thereof.

13. The composition of claim 12, wherein said carrier is lactose.

14. The composition of claim 12, wherein said carrier is magnesium stearate.

15. The composition of claim 1, additionally comprising croscarmellose sodium.

16. The composition of claim 1, being present in the form of a tablet.

17. The composition of claim 1, being present in the form of a capsule.

18. The composition of claim 1, being present in the form of a liquid.

19. The composition of claim 18, wherein said liquid is a solution of said composition in a suitable solvent.

20. The composition of claim 16, wherein said tablet is prepared by compression.

21. The composition of claim 16, wherein said tablet is prepared by granulation.

22. The composition of claim 1, wherein said antihistamine is present in amounts in the range 2-20 milligrams per dosage.

23. The composition of claim 1, wherein said antihistamine is present in amounts in the range 2-10 milligrams per dosage.

24. The composition of claim 1, wherein said antihistamine is present in about 3-7 milligrams amounts per dosage.

25. The composition of claim 1, wherein said glucocorticoid is present is about 0.02-1 milligram per dosage.

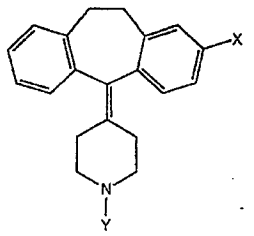
26. The composition of claim 1, wherein said glucocorticoid is present is about 0.02-0.8 milligram per dosage.

27. The composition of claim 1, wherein said glucocorticoid is present is about 0.03-0.5 milligram per dosage.

28. The composition of claim 1, wherein said glucocorticoid and said antihistamine are present in a respective weight ratio range between 1:100 and 1:10.

29. A method for the treatment of atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, and allergic reaction to insect stings and bites, in a mammalian organism in need of such treatment, said method comprising administering to said organism a composition comprising: (i) a therapeutically effective amount of one or more substantially non-sedating antihistamines or a pharmaceutically acceptable salt or solvate thereof; and (ii) a therapeutically effective amount of one or more glucocorticoid.

30. The method of claim 29, wherein said antihistamine corresponds to the general formula:



wherein X represents a halogen atom or a hydrogen atom; and Y represents hydrogen, $-COOR_1$ or $-SO_2R_2$, wherein R_1 represents a substituted or unsubstituted alkyl group,

a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heterocyclic ring; and R_2 represents a substituted or unsubstituted cycloalkyl group, or substituted or unsubstituted aryl group as well as optical isomers and mixtures of said antihistamine.

31. The method of claim 30, wherein X is Cl and Y is $-COOC_2H_5$, said antihistamine being known as loratadine.

32. The method of claim 29, wherein said glucocorticoid is selected from the group consisting of prednisolone, prednisone, betamethasone, dexamethasone, fluoromethalone, medrysone, triamcinolone, hydrocortisone, prednicarbate, deflazacort, halomethasone, tixocortol, predinylidene (21-diethylaminoacetate), prednival, paramethasone, methylprednisolone, meprednisone, mazipredone, isoflupredone, halopredone acetate, halcinonide, formocortal, flurandrenolide, fluprednisolone, fluprednine acetate, fluperolone acetate, fluocortolone, fluocortin butyl, fluocinonide, fluocinolone acetonide, flunisolode, flumethasone, fludrocortisone, enoxolone, difluprednate, diflucortolone, diflorasone diacetate, desoxymetasone, desonide, cortivazol, corticosterone, cortisone, cloprednol, clocortolone, clobetasone, clobetasol, chloroprednisone, cafestol, budesonide, beclomethasone, amcinonide, allopregnane acetonide, alclometasone, 21-acetoxypregnenolone, tralonide, diflurasone acetate, deacylcortivazol, budesonide, deacylcortivazol oxetanone, and mixtures thereof.

33. The method of claim 32, wherein said glucocorticoid is betamethasone.

34. A pharmaceutical composition for the treatment of atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, and allergic reaction to insect stings and bites, said composition comprising: (i) a therapeutically effective amount of loratadine or a pharmaceutically acceptable salt or solvate thereof; (ii) a therapeutically effective amount of betamethasone; and (iii) lactose.

35. The composition of claim 34, additionally comprising magnesium stearate and croscarmellose sodium.

36. A method for the treatment of atopic dermatitis, angioedema, urticaria, seasonal and allergic rhinitis, food and drug allergies, allergic contact dermatitis, seborrhoic dermatitis, neurodermatitis, allergic asthma, ocular allergic manifestations such as conjunctivitis and iridociclitis, and allergic reaction to insect stings and bites, in a mammalian organism in need of such treatment, said method comprising

administering to said organism a composition comprising: (i) a therapeutically effective amount of loratadine or a pharmaceutically acceptable salt or solvate thereof; (ii) a therapeutically effective amount of betamethasone; and (iii) lactose.

37. The method of claim 36, wherein said composition additionally comprises magnesium stearate and croscarmellose sodium.

INTERNATIONAL SEARCH REPORT

International Application No
PC./US 99/04502

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K31/57 //(A61K31/57,31:445)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 704 206 A (REGENOLD JUERGEN DR) 3 April 1996 (1996-04-03) *cf. claims 1 and 29*	1-37
X	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 (1997-06-25) *cf. abstract, page 3, lines 15-30, page 5, example 1, claim 1*	1-37
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1999	24/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stoltner, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC./US 99/04502

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JEAL W. ET AL.: "Triamcinolone acetonide. A review of its pharmacological properties and therapeutic efficacy in the management of allergic rhinitis" DRUGS, vol. 53, no. 2, February 1997 (1997-02), pages 257-280, XP002121955 *cf. page 258, lines 16-21, page 260, 19-21, page 273, 4th para. on the right-handed col., page 274, left col., 2nd para..*	1-37
X	RATNER P. H., ET AL.: "A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis" JOURNAL OF FAMILY PRACTICE, vol. 47, no. 2, August 1998 (1998-08), pages 118-125, XP002121956 *cf. page 118, "background", right-handed col., 2nd para., bridging with page 119, left col., 1st para., page 120, table 1, page 121, figure 1 and page 124, left-hand col., 3rd para.,*	1-37

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PC., US 99/04502

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0704206 A	03-04-1996	CA 2201358 A	11-04-1996
		WO 9610389 A	11-04-1996
		DE 19536244 A	04-04-1996
		DE 19536245 A	04-04-1996
		DE 19536246 A	04-04-1996
		US 5958379 A	28-09-1999
EP 0780127 A	25-06-1997	NONE	

Form PCT/ISA/210 (patent family annex) (July 1992)